REMARKS

Claims 1, 2, 21, 22, and 48-67 are pending in the application. No amendments have been made by the present response.

Request for Withdrawal of Finality of the Office Action

A non-final Office Action was mailed for the present application on January 9, 2009. Applicants filed a response to the action on July 9, 2009. That response contained amendments that incorporated the limitations of previously examined dependent claim 18 into independent claims 1 and 51. The present Office Action was made final and contains several new grounds of rejection. The present Office Action states that applicants' amendment necessitated the new grounds of rejection.

Previous dependent claim 18 was directed to a method of reducing or preventing oxidative stress-associated cell death in an individual diagnosed as having had a myocardial infarction or stroke. Claim 18 was cancelled by the previous amendment and its limitations were incorporated into independent claims 1 and 51 as follows: claim 1 is directed to a method of treating a myocardial infarction; and claim 51 is directed to a method of treating a stroke.

MPEP §706.07(a) states that a "second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement..." (emphasis added). Applicants' amendments in the response to the previous office action did not necessitate any of the new rejections. The previous amendment merely incorporated subject matter of a cancelled dependent claim into the independent claims. As a result, and as is required by MPEP §706.07(a), the new rejections contained in the present office action should not have been presented in a final action. The MPEP passage reproduced above protects applicants from having to face, under the severe procedural limitations of a final office action, new grounds of rejection that could have been introduced in a prior non-final action but are instead being presented for the first time, through no fault of applicants, in a final rejection. All of the new rejections and objections could have been presented in the prior non-final Office Action.

In view of the introduction of new grounds of rejection that were neither necessitated by applicants' amendment of the claims nor based on information submitted in an information disclosure statement, applicants request that the finality of the present Office Action be withdrawn.

35 U.S.C. §103(a) (Obviousness)

At pages 3-5 of the Office Action, claims 1, 2, 22, 51, 53, 58, 62, and 64 were finally rejected as unpatentable over Gambacorti-Passerini et al., WO 01/47507 ("Gambacorti") in view of Kumar et al. (2001) J. Biol. Chem 276:17281-85 ("Kumar"), Kufe et al., U.S. Patent No. 7,118,862 ("Kufe"), and Fraley et al, U.S. Patent No. 6,306,874 ("Fraley").

Independent claims 1 and 51 are directed to methods of treating a myocardial infarction (claim 1) or a stroke (claim 51) by administering to an individual in need thereof a therapeutically effective amount of a composition comprising an N-phenyl-2-pyrimidine-amine. Myocardial infarction and stroke are disorders characterized by excessive oxidative stress-associated cell death.

As detailed in the previous response to Office Action, the claimed methods are based at least in part on the inventors' discovery that the tyrosine kinase inhibitor STI571 can be used to prevent cell death associated with oxidative stress. STI571 was previously known to be highly effective in the treatment of chronic myelogenous leukemia ("CML") and to induce apoptosis of CML cells in culture. In contrast, the experimental data contained in the present application demonstrates that STI571 inhibits ROS-induced apoptosis. The finding that STI571 inhibits apoptosis was unexpected in light of the molecule's prior characterization as an effective inducer of apoptosis in cells derived from CML patients.

Nothing in Gambacorti or any of the other cited references would have led the person of ordinary skill in the art to reasonably expect that STI571 would inhibit apoptosis and be effective in the treatment of myocardial infarction and stroke. Gambacorti discloses the use of STI571 for the treatment of proliferative diseases. Gambacorti (at page 37, last paragraph extending to the top of page 38) reflects the understanding, at the time the present application was filed, that STI571 was a compound that induces apoptosis:

> STI571 (formerly known as CGP57148) represents an active and relatively specific inhibitor of bcr/abl kinase activity. STI571 blocks proliferation and induces apoptosis in BCR/ABL+ cells *in vitro*; it inhibits the growth of clonogenic bone marrow cells obtained from CML patients, and can eradicate leukemic cell growth *in vivo*. (emphasis added)

The person of ordinary skill in the art having read Gambacorti would have had no reason to expect that a compound (such as STI571) that induces apoptosis (and is useful for treating disorders such as proliferative diseases that are characterized by insufficient cell death) would be useful in inhibiting apoptosis and treating disorders characterized by excessive oxidative stress-associated cell death. If anything, Gambacorti teaches away from using STI571 to treat disorders, such as myocardial infarction and stroke, that are characterized by excessive oxidative stress-associated cell death.

Kumar and Kufe do not cure the deficiencies of Gambacorti. Kufe is the patent counterpart of the Kumar academic publication (i.e., the experimental results of Kumar are described within Example 4 of Kufe). Kumar and Kufe describe the discovery that c-Abl is targeted to the mitochondria in the cell death response to oxidative stress. Kumar and Kufe describe the importance of mitochondrial localization of c-Abl to cell death processes, but provide no hint that inhibition of c-Abl activity may be an effective means of preventing cell death associated with oxidative stress. Because c-Abl is present in cellular compartments in addition to the mitochondria, the person of ordinary skill in the art would not have expected that global inhibition of c-Abl activity in a cell (e.g., by treatment with STI571) would be an effective means of treating disorders characterized by excessive oxidative stress-associated cell death. Consistent with the notion that the skilled artisan would not have made the leap suggested in the Office Action, the section of the Kufe patent specification that details methods of screening for candidate therapeutic compounds describes screenings assays and methods of treatment based on the modulation of translocation of c-Abl to the mitochondria. Kufe at column 8, line 51, to column 10, line 21. Nowhere does Kufe propose inhibiting c-Abl kinase activity as a means of modulating oxidative stress-associated cell death. Kufe's silence on the entire concept of inhibiting c-Abl enzymatic activity, which is significantly easier to achieve than inhibiting mitochondrial translocation of c-Abl, is a clear indication that inhibition of c-Abl activity was

not considered an appropriate means to prevent cell death associated with oxidative stress and treat disorders such as myocardial infarction and stroke.

Fraley describes a class of compounds that are stated to be inhibitors of tyrosine kinase activity. Within Fraley's extensive list of asserted "utilities" for the disclosed compounds, Fraley states that the compounds may be used "to reduce or prevent tissue damage which occurs after cerebral ischemic events, such as stroke." Fraley at column 19, lines 48-53. Nothing in Fraley would have led the skilled person to reasonably expect that a compound that inhibits c-Abl kinase activity (such as STI571) would be effective in the treatment of stroke. As an initial matter, nothing in Fraley suggests that the compounds described therein inhibit c-Abl. Second, there is no experimental evidence in Fraley that would have led the person of ordinary skill in the art to conclude that even the compounds disclosed therein are effective in the treatment of stroke. The mere listing in a patent specification, without supporting experimental evidence, of a list of disorders that are stated to be treatable with a compound would not have led to such an expectation. Fraley would not have led the skilled artisan to reasonably expect that any compound that inhibits any tyrosine kinase would be effective in treating stroke.

As a result, the combined teachings of Gambacorti, Kumar, Kufe, and Fraley would not have led the person of ordinary skill in the art at the time the present application was filed to reasonably expect that STI571 could be used in the treatment of myocardial infarction and stroke, disorders characterized by excessive oxidative stress-associated cell death.

In view of the foregoing, Gambacorti, Kumar, Kufe, Fraley do not render obvious independent claims 1 or 51 or the claims that depend directly or indirectly therefrom. Applicants respectfully request that the Examiner withdraw the rejection.

At pages 5-6 of the Office Action, claims 21, 48, 49, 52, 54, 55, 57, 59, 60, 63, 65, and 66 were finally rejected as unpatentable over Gambacorti in view of Kumar, Kufe, Fraley, and Tamao et al., U.S. Patent No. 5,141,947 ("Tamao").

The Office Action cited Tamao as allegedly describing features of various dependent claims and asserted that it would have been obvious to modify the methods of Gambacorti in view of Kumar, Kufe, Fraley, and Tamao to arrive at the methods of these dependent claims.

As detailed above, the combination of Gambacorti, Kumar, Kufe, and Fraley does not render obvious the methods of independent claims 1 and 51. Tamao provides nothing that supplements the deficiencies of Gambacorti, Kumar, Kufe, and Fraley or renders obvious the methods of independent claims 1 and 51. Accordingly, once independent claims 1 and 51 are held allowable, dependent claims 21, 48, 49, 52, 54, 55, 57, 59, 60, 63, 65, and 66 should also be in condition for allowance.

At pages 7-8 of the Office Action, claims 50, 56, 61, and 67 were finally rejected as unpatentable over Gambacorti in view of Kumar, Kufe, Fraley, and Stern et al., U.S. Patent No. 5,426,097 ("Stern").

The Office Action cited Stern as allegedly describing features of various dependent claims and asserted that it would have been obvious to modify the methods of Gambacorti in view of Kumar, Kufe, Fraley, and Stern to arrive at the methods of these dependent claims.

As detailed above, the combination of Gambacorti, Kumar, Kufe, and Fraley does not render obvious the methods of independent claims 1 and 51. Stern provides nothing that supplements the deficiencies of Gambacorti, Kumar, Kufe, and Fraley or renders obvious the methods of independent claims 1 and 51. Accordingly, once independent claims 1 and 51 are held allowable, dependent claims 50, 56, 61, and 67 should also be in condition for allowance.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 00530-0108US1.

Respectfully submitted,

Date: January 19, 2010

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